HALOGENATED SOLVENTS INDUSTRY ALLIANCE, INC

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June 22, 2001

Document Control Office (7407)
Office of Pollution Prevention and Toxics
Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Re: OPPTS-00274D – Sponsorship Commitments for Trichloroethylene (CAS No. 79-01-6) and Tetrachloroethylene (CAS No. 127-18-4)

Dear Sirs:

I am writing on behalf of the Halogenated Solvents Industry Alliance, Inc. (HSIA), which represents the U.S. producers of trichloroethylene (TCE) and tetrachloroethylene (perc). On behalf of these companies, HSIA commits to sponsor TCE and perc in Tier I of the pilot Voluntary Children's Chemical Evaluation Program (VCCEP). 65 Fed. Reg, 8 1700-7 18 (Dec. 26, 2000).

HSIA intends to fulfill this commitment in two stages. The first stage will be by execution and implementation of memoranda of understanding (MOUs) with the Agency for Toxic Substances and Disease Registry (ATSDR), pursuant to which HSIA will agree to conduct specified toxicity testing. A copy of a letter to ATSDR identifying the studies HSIA will be conducting to address ATSDR's priority data needs for TCE and perc is enclosed, It is intended that those MOUs would be signed within six months of the date of this letter, The start dates for the toxicity testing and submission dates for the final reports shall be as specified in the MOUs.

At the second stage, HSIA commits to develop hazard assessments of Tier I and existing higher-tier studies of TCE and perc (including the studies to be conducted under the MOUs). In addition, HSIA commits to develop exposure assessments that meet or exceed the requirements for a Tier I Exposure Assessment specified by EPA (65 Fed, Reg. At 8 17 11). HSIA further commits to develop risk assessments which integrate these hazard and exposure assessments and characterize the potential risks to children posed by TCE and perc based on the quality and extent of the available data. HSIA will also

prepare data needs assessments that include weight-of-the-evidence evaluations of the available hazard and exposure information and assess whether additional information is needed in order to evaluate the potential risk to children. These will be prepared and submitted in a timely fashion following completion of the toxicity testing and acceptance of the test results by ATSDR.

Finally, HSIA will prepare Peer Consultation Documents for TCE and perc consisting of the four components identified above and will provide three hard copies and an electronic copy of each to EPA. We understand that EPA will make the Documents available to a third-party scientific organization which will distribute them to the Peer Consultation Group and present the assessments and recommendations to the Group. It is anticipated that the Peer Consultations will result in reports to EPA (to be prepared by the third-party contractor) which will include recommendations as to whether further testing or evaluation of TCE and perc under the VCCEP is or is not necessary.

As part of the foregoing activities, HSIA commits (i) to judge existing studies not conducted under Good Laboratory Practices (GLP) guidelines based on their merits, (ii) to generate any new hazard data under GLPs and current EPA test guidelines as of the date the testing is initiated, and (iii) to make the hazard and exposure data developed publicly available. Should elements of the VCCEP pilot change in the future, HSIA reserves the right to adjust its commitment accordingly.

In making this commitment, HSXA is acting *voluntarily* and not in response to any legally enforceable mandate, At the same time, HSIA emphasizes that EPA has recognized that identification of TCE and perc in the VCCEP pilot "does not mean that EPA has made or will make a determination that any uses of the chemical pose significant risks to children's health," and that "EPA may ultimately determine that reasonably anticipated exposures and risks from expected uses do not pose any unique or other concerns for children's health and safety" (65 Fed. Reg. At 81702).

We trust that this letter is sufficient to express our commitment to sponsor TCE and perc in the first tier of the VCCEP pilot. This commitment is made on behalf of the following companies:

Vulcan Materials Company

The Dow Chemical Company

PPG Industries, Inc.

INEOS Chlor Americas, Inc.

I will serve as technical contact for HSIA. My contact numbers and e-mail address are as follows:

(202) 775-0232 (phone)
(202) 833-0381 (fax)
pdugard@hsia.org

Please do not hesitate to contact me if there are any questions about this commitment,

Sincerely yours,

Paul H. Dugard, Ph.D.
Director of Scientific Programs

Enclosure

cc: Mr. Charles M. Auer
Christopher DeRosa, Ph.D.
William Cibulas, PhD.
W. Caffey Norman, Esq.

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June 22, 2001

Christopher T. DeRosa, PhD
Director, Division of Toxicology
Agency for Toxic Substances and Disease Registry
1600 Clifton Road (E29)
Atlanta, GA 30333

ATSDR PRIORITY DATA NEEDS FOR TRICHLOROETHYLENE AND TETRACHLOROETHYLENE

Dear Dr. DeRosa:

The Halogenated Solvents Industry Alliance, Inc. (HSIA) has previously discussed with you a voluntary program to satisfy priority data needs (PDNs) for trichloroethylene and tetrachloroethylene identified by ATSDR. The most recently published listing of PDNs for trichloroethylene (TCE) and tetrachloroethylene (perc) appeared in the Federal Register of January 15, 1999 (64 FR 2760-2790). This letter reflects HSIA's intention to sponsor testing to fill PDNs identified for these chemicals that involve toxicity studies.

Trichloroethylene

PDN Number 1 Ob: '"Neurotoxicology battery of tests via the oral route", In the Federal Register notice, the program to fill this PDN is assigned to the Minority Health Professions Foundation (MHPF) but this organization is not now expected to conduct these studies. Since high quality studies of TCE administered via the inhalation route are available, HSIA will bridge between the inhalation route (rodent) and the oral route (human) using physiologically-based pharmacokinetic (PB-PK) modeling (see below for a general explanation).

PDN No. 10c: "Immunotoxicology battery of tests via the oral route". HSIA will conduct an appropriate study of the immunotoxic potential of TCE, exact details to be agreed with ATSDR. This study is likely to employ oral administration.

PDN No. 1 Of: "Dose response data in animals for intermediate-duration oral exposure" with a footnote indicating that this PDN has arisen because of "withdrawal of intermediate oral Minimal Risk Level (MRL) from ATSDR's *Toxicological Profile for Trichloroethylene.*"
There are existing studies involving inhalation exposure for the "intermediate" duration and HSIA expects that PB-PK modeling will provide a suitable means of bridging to the oral route. It is also likely that studies to be conducted by HSIA will provide data for the calculation of an intermediate duration MRL via the oral route.

PDN No. 1 0g: "l-species developmental toxicity study via oral exposure" with a footnote indicating "Study to be conducted with special emphasis on developmental neurotoxicity".
HSIA is already addressing the data need for a developmental toxicity study by sponsoring a rat inhalation study that meets EPA guidelines. As agreed with ATSDR in a Memorandum of Understanding (MoU), the dose levels in this study will be extrapolated to the oral route by means of PB-PK modeling. HSIA will address the PDN for developmental neurotoxicity by sponsoring a study in rats, probably employing the oral route (see caveat below regarding the study design).

Tetrachloroethylene

PDN No. 13 b: "Multigeneration reproductive study via oral exposure."
HSIA has completed a multigeneration study in rats with exposures via the inhalation route. HSIA will bridge from the inhalation dose levels in this study to the oral route using PB-PK. modeling.

PDN No. 13 c: "Dose response data in animals for intermediate-duration oral exposure, including neuropathology and demeanor, and immunopathology" with a footnote indicating that this PDN has arisen because of "withdrawal of intermediate oral MRL from ATSDR's *Toxicological Profile for Tetrachloroethylene*".
High quality inhalation neurotoxicity studies in the rat already exist, and HSIA will extrapolate the dose levels in these studies to the oral route.
HSIA will investigate the immunotoxic potential of perc in a screening study that meets EPA guidelines. This will be conducted using the oral route, or possibly, the inhalation route with PB-PK based dose conversion to the oral route.

PDN No. 13d: "l-species developmental toxicity study via oral route" with a footnote indicating "Study to be conducted with special emphasis on developmental neurotoxicity".
HSIA will address this PDN with two studies. The first will be a standard guideline developmental toxicity study in rats, probably using the inhalation route (with PB-PK modeling to extrapolate to the human oral route). The second study will address potential developmental neurotoxicity in rats, probably employing the oral route (see caveat).

General Comments on Response to PDNs

ATSDR and HSIA have established that, where suitable models are available, extrapolation between routes of administration and between species can be achieved using PB-PK modeling. This was demonstrated in the ATSDR-HSIA program for methylene chloride. Since robust **PB-PK** models exist for both TCE and perc, the use of PB-PK modeling as indicated above should prove to be scientifically valid and an acceptable means of filling PDNs.

The EPA guideline for developmental neurotoxicity studies is currently evolving and is also the subject of a legal challenge. HSIA would prefer to follow a stable, generally accepted EPA guideline for this type of study. Given the current uncertainty, HSIA reserves the right to review the status of the guideline at the stage of protocol development for each of the solvents.

Although the timelines included with this letter show exposure and risk assessments, HSIA's commitment to the Voluntary Children's Chemical Evaluation Program (VCCEP) will require those analyses to be submitted to the peer consultation process of VCCEP. Because of this commitment to the **VCCEP,** HSIA does not plan to submit the exposure or risk assessments to **ATSDR** formally but will keep ATSDR informed of progress and discuss scientific issues, as appropriate.

Memoranda of Understanding

This letter expresses HSIA's current intent, recognizing that MoUs will need to be developed for each of the solvents to define further the two programs, We anticipate that MoUs can be completed and signed within 6 months of the date of this letter. Testing would be initiated and study reports submitted to ATSDR in general accordance with the enclosed timelines, subject to modification in the MoUs and other modifications that HSIA and ATSDR agree are mutually desirable.

Relationship to EPA's Voluntary Children's Chemical Evaluation Program

HSIA is making a commitment to sponsor each of the solvents in Tier I of the VCCEP pilot. If the testing program outlined in this letter, in your view, satisfies ATSDR's requirements for PDNs for these chemicals,, I would appreciate your so notifying Mr. Charles Auer of EPA by June 25, 2001, the deadline for submission of sponsorship commitments. HSIA's letter to EPA of today's date is enclosed.

We look forward to continuing a productive collaboration with ATSDR.

Yours sincerely,

Paul H. Dugard, PhD
Director of Scientific Programs

Enclosures

cc: Mr. Charles M. Auer
William Cibulas, PhD
W. Caffey Norman, Esq.

Perchloroethylene: Probable HSIA/ATSDR Voluntary Program

Activity/ Study	2001	2002	2003	2004	2005	2006	2007
Developmental (Rat Inhalation)	Initiate	Experimental	Report				
Develop PBPK Models (Rat, Mouse, Man)		Initiate	Experimental	Report			
Apply PBPK to Existing Studies: Reproductive Neurotoxicity Subchronic		Initiate	Experimental	Report			
Apply PBPK to Rat Developmental				Initiate	Experimental/ Report		
Immunotoxicity (Rat Inhalation)			Initiate	Experimental	Report		
Apply PBPK to Rat Immunotoxicity					Initiate	Experimental/ Report	
Developmental Neurotoxicity (Rat Oral?)				Initiate	Experimental	Report	
Exposure Assessment					Initiate	Experimental	Report
Risk Assessment						Initiate	Experimental/ Report

NOTE: Indication is of year in which events occur and not specific start date or duration. Studies to final, stable EPA guidelines unless otherwise agreed.

INITIATE = Select laboratory or contractor, draft protocol, per review of protocol, response to peer review.
EXPERIMENTAL = Laboratory experiment or contractor work on project.
REPORT = Prepare draft report, peer review, response to peer review, submit final report

Trichloroethylene: Probable HSIA/ATSDR Voluntary Program

Activity/ Study	2001	2002	2003	2004	2005	2006	2007
Developmental (Rat Inhalation)	Report						
Develop PBPK Models (Rat, Mouse, Man)	Initiate	Experimental	Report				
Apply PBPK to Existing Studies: Neurotoxicity Subchronic	Initiate	Experimental	Report				
Apply PBPK to Rat Developmental		Initiate	Experimental/ Report				
Immunotoxicity (Rat Inhalation)		Initiate	Experimental	Report			
Apply PBPK to Rat Immunotoxicity			Initiate	Experimental/ Report			
Developmental Neurotoxicity (Rat Oral?)			Initiate	Experimental	Report		
Exposure Assessment				Initiate	Experimental	Report	
Risk Assessment					Initiate	Experimental	Report

NOTE: Indication is of year in which events occur and not specific start date or duration. Studies to final, stable EPA guidelines unless otherwise agreed.

INITIATE = Select laboratory or contractor, draft protocol, peer review of protocol, response to peer review.
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